Methemoglobinemia in a 28-year-old woman treated with dapsone

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■ Cite as: *CMAJ* 2022 August 8;194:E1062-5. doi: 10.1503/cmaj.212015

A 28-year-old woman presented to the emergency department with a 4-day history of shortness of breath and fatigue.

The patient had received a diagnosis of immunoglobulin A (IgA) nephropathy 1 month previously, after presenting with a creatinine level of 558 (normal 50–110) µmol/L, nephrotic range proteinuria and consistent histology on kidney biopsy. She received 3 days of treatment with methylprednisolone (1 g once daily) and then a weaning course of oral prednisone (starting at 60 mg/d). She was also prescribed trimethoprim–sulfamethoxazole (800 mg/160 mg orally 3 times weekly) as prophylaxis for pneumonia caused by the fungus *Pneumocystis jirovecii*. A rash developed 12 days before this presentation, which was attributed to trimethoprim–sulfamethoxazole, and she was prescribed dapsone (100 mg/d taken orally), a second-line anti-biotic for pneumocystis pneumonia prophylaxis, instead.

On examination, the patient had central cyanosis, was not in respiratory distress and was hemodynamically stable. Cardiac and pulmonary examinations were unremarkable and her oxygen saturation level was 89%–91% on room air and 91% on supplemental oxygen (10 L/min).

Results from her bloodwork reported a hemoglobin level of 55 (normal 120–160) g/L, mean corpuscular volume of 93.6 (normal 80–100) fL, lactate dehydrogenase level of 776 (normal 45–90) IU/L, haptoglobin level of less than 0.10 (normal 0.16–2.20) g/L, reticulocyte count of 293 (normal 25–75) × 10^9/L and creatinine level of 820 µmol/L (Table 1). A peripheral smear showed fragmented erythrocytes (Figure 1). Coagulation studies, direct antibody testing and serum electrolytes were normal. Findings from radiography of her chest were unremarkable.

The emergency department physician considered methemoglobinemia, given the history of dapsone exposure, low oxygen saturation levels with no improvement on supplemental oxygen and normal chest radiograph. A venous blood gas analysis found raised methemoglobin levels of 15.9% (normal 0.4%–1.2%), with normal carboxyhemoglobin levels.

We consulted the hematology team, who considered thrombotic thrombocytopenia purpura; however, platelet count remained stable and the *ADAMTS13* activity was normal at 87% (41%–130%). They ruled out autoimmune hemolytic anemia and disseminated intravascular coagulation owing to normal coagulation studies and a normal direct antibody test. A lack of symptoms of infection suggested that the patient did not have hemolytic uremic syndrome. Based on the history and laboratory findings, the hematology team diagnosed probable dapsone-induced hemolytic anemia, and requested glucose-6-phosphate dehydrogenase (G6PD) testing.

After consultation with the Ontario Poison Centre, we stopped dapsone and started transfusion of erythrocytes to target a hemoglobin level of above 70 g/L. We prescribed oral cimetidine (300 mg every 8 h). We did not prescribe methylene blue owing to the patient's unknown G6PD status, active hemolysis and clinical stability.

In consultation with the hematology team, we stopped cimetidine on day 3. By day 6, the patient's oxygen saturation levels were 96% on room air and her methemoglobin level had decreased to 1.6%. Her G6PD level returned to 19.4 (8.3–17.0) IU/g Hb. However, hemolysis persisted, and blood transfusions on days 4, 6 and 13 were required. During her hospital admission, the patient's estimated glomerular filtration rate decreased to 6 mL/min/m^2, her peripheral edema worsened and she was started on hemodialysis for end-stage kidney disease from IgA nephropathy. The prednisone used to treat the IgA nephropathy was tapered over 4 weeks and then stopped.

Key points

- The sulfone antibiotic dapsone, at prophylactic doses, can be associated with the development of methemoglobinemia and hemolytic anemia in patients with and without glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Risk factors for the development of symptomatic methemoglobinemia and hemolytic anemia include underlying anemia, cardiorespiratory disease and G6PD deficiency.
- Methemoglobinemia should be suspected in the presence of cyanosis with low oxygen saturation and normal partial pressure of oxygen in the arterial blood; confirmation is obtained by evaluating methemoglobin levels.
- Methylene blue is used in the treatment of dapsone-induced methemoglobinemia, but it may be contraindicated in patients with hemolysis; cimetidine is an alternative option.

Table 1: Laboratory results

Laboratory test	Patient results				Normal
	1 month before presentation	This presentation	1 month after discharge	4 months after discharge	
Hemoglobin, g/L	106	55	82	104	120–160
MCV, fL	81.7	93.6	89.7	88.6	80–100
White blood cells, × 10^9/L	9.1	11.1	9.9	5.9	3.5–12.0
Platelets, × 10^9/L	283	162	327	257	150–400
Lactate dehydrogenase, IU/L	776	776		170	45–90
Haptoglobin, g/L	0.42	< 0.10		0.74	0.16–2.2
Reticulocyte count, × 10^9/L	68	293		84	25–75
International normalized ratio		1.0		1.0	0.9–1.1
Partial thromboplastin time, s		20		24	20–29
Creatinine, µmol/L	558	820	913	889	50–110
Urea, mmol/L	39.5	51.1	20.2	26.7	< 8.3
Alanine aminotransferase, U/L	13	15		7	< 33
Aspartate aminotransferase, U/L	10	19		12	< 32
Alkaline phosphatase, U/L	70	55		54	35–104
Venous blood gas pH		7.46			7.32–7.42
Venous blood gas pCO_2, mm Hg		31			38–50
Venous blood gas lactate		1.5			
Venous blood gas methemoglobin, %		15.9			0.4–1.2
Venous blood gas carboxyhemoglobin, %		2.0			< 1.5
ADAMTS13, %		87			41–130
G6PD IU/g Hb		19.4		15.8	8.3–17.0

Note: G6PD = glucose-6-phosphate dehydrogenase, MCV = mean corpuscular volume.

The patient was discharged on day 13 with oxygen saturation levels of 95%–97% on room air and a stable hemoglobin level of 72 g/L. We were able to follow-up with her at her dialysis sessions that occurred 3 times per week. We started darbopoietin (20 µg weekly administered subcutaneously) and intravenous iron for anemia secondary to end-stage kidney disease targeting a hemoglobin level of 95–115 g/L. Three months after discharge, the patient's hemoglobin level was 104 g/L. Repeat testing for G6PD activity was normal.

Discussion

Dapsone, a sulfone antibiotic that inhibits folate synthesis, is increasingly prescribed, predominantly for a range of dermatologic conditions, including leprosy and dermatitis herpetiforms, but also for nondermatologic indications, including pneumocystis pneumonia prophylaxis and treatment.[1]

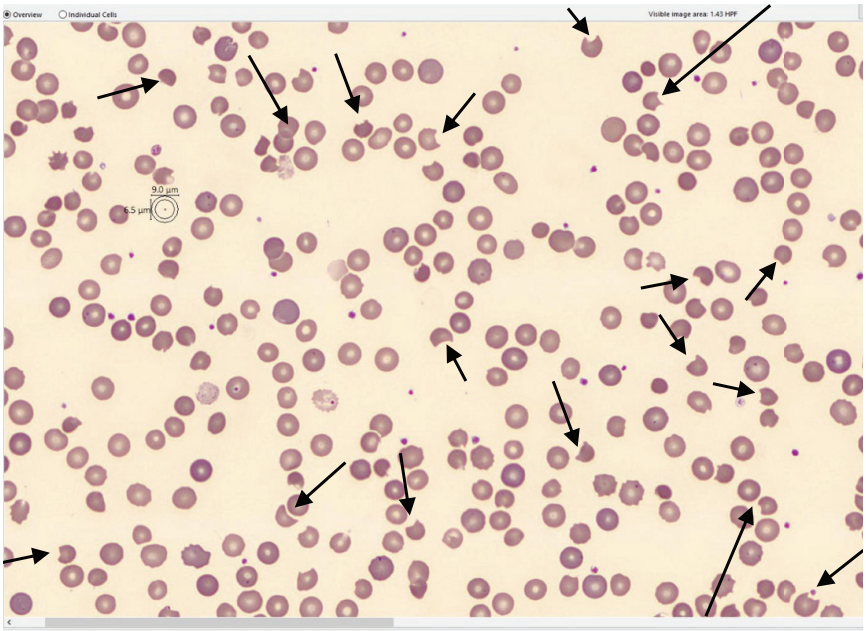

Figure 1: Blood smear taken upon hospital admission showing fragmented erythrocytes (arrows), which have the characteristic "bite cell" appearance.

Pneumocystis pneumonia is an opportunistic infection affecting people who are immunocompromised. Few studies have looked at pneumocystis pneumonia prophylaxis in patients with autoimmune or inflammatory diseases on immunosuppression; thus, pneumocystis pneumonia prophylaxis in this setting is largely based on expert opinion.

In patients who do not have HIV, pneumocystis pneumonia prophylaxis is suggested for people with a risk of pneumocystis pneumonia of greater than 6.2%, based on a meta-analysis involving patients with hematologic malignant disease or organ transplant, where the number needed to treat to prevent 1 pneumocystis pneumonia infection was 19.[2] Pneumocystis pneumonia prophylaxis is suggested for patients prescribed prednisone (> 20 mg) for more than 1 month for high-risk conditions, such as granulomatosis with polyangiitis and connective tissue disease with interstitial lung disease.[3] Pneumocystis pneumonia prophylaxis should be considered for patients with intermediate risk conditions, including antineutrophil cytoplasmic autoantibody vasculitis and connective tissue disease with renal involvement.[3]

Despite risks associated with prophylaxis, the risks of pneumocystis pneumonia outweigh the risks of the prophylactic treatment, since it tends to cause more severe, rapidly progressive and life-threatening disease in patients who do not have HIV.[3] Although first-line therapy is trimethoprim–sulfamethoxazole, a systematic review found that as many as 3 in 100 patients have adverse drug reactions that lead to drug withdrawal, including leukopenia, thrombocytopenia and rashes, as in this case.[2] Dapsone is second-line therapy, and is being used more frequently, which underscores the importance of recognizing its potential adverse effects.

Dapsone reaches peak concentration 2–6 hours after ingestion, with a half-life of 20–30 hours.[4] It is metabolized by the liver by way of acetylation to inactive metabolites and by cytochrome P450 enzymes to the toxic metabolite, dapsone hydroxylamine. This metabolite undergoes enterohepatic recirculation and is rapidly taken up by erythrocytes, which can lead to hemolysis and methemoglobinemia.[4] Adverse events are typically dose dependent and more likely to cause symptoms in patients with underlying anemia, cardiorespiratory disease or G6PD deficiency.[5]

Methemoglobinemia is typically acquired by exposure to medications, including dapsone and benzocaine spray, overdose with amyl nitrate and sodium nitrite or certain medical conditions, including sepsis and sickle cell crisis, and, in the pediatric population, dehydration.[6] In a 2004 retrospective study, dapsone was the cause in 42% of cases of acquired methemoglobinemia (mean methemoglobin level 7.6%), whereas benzocaine was a less common cause (20%) but resulted in higher methemoglobin levels (43.8%).[6] Limited evidence suggests that hemolytic anemia or methemoglobinemia develops in about 4%–13% of patients who are given dapsone.[4] One case–control study reported hemolysis in 5.8% of recipients of hematopoietic stem cell transplants who received prophylactic dapsone, and hemolysis with methemoglobinemia in 3.2% of the cohort.[7]

In a case series involving 6 patients given dapsone, all patients had elevated methemoglobin levels after 2 weeks of treatment.[8] However, methemoglobin levels are not routinely checked after starting dapsone, which leaves the exact incidence of asymptomatic methemoglobinemia from dapsone use unclear. The onset of methemoglobinemia after starting dapsone is variable: 1 study involving 16 patients who underwent solid organ transplant and were receiving prophylactic dapsone reported that methemoglobinemia presented at a median 48 (range 7–809) days after treatment began.[3] In this case, the patient presented 12 days after starting dapsone.

Typically, methemoglobin levels are suppressed (< 1% of total hemoglobin) by protective enzymes. However, when those enzymes are overwhelmed or dysfunctional, as in G6PD deficiency, or if erythrocytes are exposed to oxidative stress, by way of exposure to toxic metabolites of drugs such as dapsone, hemoglobin converts to methemoglobin. As methemoglobin cannot bind oxygen, a left shift in the oxygen dissociation curve results, which leads to decreased oxygen delivery to tissues.[4]

The most common feature of methemoglobinemia is refractory hypoxemia with a discrepancy between noninvasive pulse oximeter (SpO_2) readings and oxygen saturation levels on arterial blood gas analysis (partial pressure of oxygen in arterial blood, PaO_2). The presence of cyanosis with low SpO_2 readings and normal PaO_2 should prompt evaluation for methemoglobinemia. Co-oximetry is a noninvasive method of measuring methemoglobin levels; however, diagnosis is typically confirmed through blood gas analysis.[4] Although a methemoglobin level of greater than 1% is abnormal, symptoms typically develop at levels greater than 20% (Table 2). In this case, the patient had dyspnea with a methemoglobin level of 15.9%; however, her comorbid anemia related to end-stage kidney disease likely contributed to her symptoms.

The main treatment for methemoglobinemia is methylene blue, which works as a cofactor for the NADPH methemoglobin reductase enzyme system to produce leukomethylene blue, which allows for the conversion of methemoglobin back to oxyhemoglobin.[4] The NADPH required for this process is generated in erythrocytes through the action of G6PD. When NADPH is decreased, such as in G6PD deficiency, methylene blue can cause hemolysis. It may also worsen dapsone-induced Heinz body hemolytic anemia.[4] In this case, based on advice from the poison centre, we opted not to use methylene blue because the patient's G6PD status was unknown, hemolysis was present and the patient was hemodynamically stable.

Table 2: Clinical manifestations of methemoglobinemia based on methemoglobin level[4]

Methemoglobin level, %	Clinical manifestations
~ 10	Cyanosis
~ 20	Headache, fatigue, tachycardia, weakness and dizziness
~ 60	Acidosis, paralysis, arrythmias, coma and seizures
~ 70	Death

Cimetidine, an H_2 receptor antagonist, is an alternative treatment for dapsone-induced methemoglobinemia. Cimetidine competes with dapsone for cytochrome P450 enzymes with decreased production of the toxic hydroxylamine metabolite, which decreases methemoglobin.[9,10] In this patient, we stopped dapsone and started cimetidine, which we continued until day 3 when the oxygen saturation levels on room air were greater than 92%. One case series found that cimetidine reduced methemoglobin levels in patients who were receiving long-term dapsone therapy within 1 week after initiation.[8] The combination of stopping dapsone and starting cimetidine may have resulted in quicker resolution of methemoglobinemia in this patient, as stoppage of dapsone alone has resulted in normalization of oxygen saturation level within 24 hours.[6]

Hemolysis after exposure to dapsone is related to the formation of Heinz bodies when heme iron is exposed to the toxic hydroxylamine metabolites of dapsone.[11] The Heinz bodies are targeted by splenic macrophages, forming the characteristic bite cells, as seen in this patient.[11] The risk of hemolysis increases in patients with G6PD deficiency because the G6PD enzyme protects erythrocytes from breaking down in the presence of oxidative stressors.[12] Results from initial G6PD testing in this patient were normal; however, enzyme activity can be normal during an acute hemolytic reaction. It is suggested that G6PD measurements are repeated at least 2 weeks to 3 months after the acute reaction.[12] The British Society for Haematology guideline for laboratory diagnosis of G6PD deficiency recommends routine screening for G6PD deficiency in any patient starting dapsone.[13] Of note, hemolysis can occur in the absence of G6PD deficiency, as occurred in this patient.

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Competing interests: None declared.

This article has been peer reviewed.

The authors have obtained patient consent.

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Contributors: All of the authors contributed to the conception of the case report and data acquisition. Gabriella Jacob drafted the manuscript. Louise Moist and Melissa Schorr revised it critically for confirmation of case details and intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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